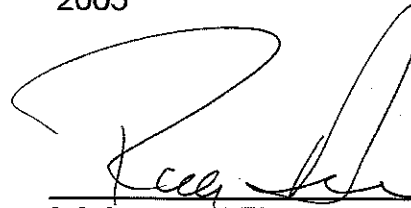


**Pulmonary Maintenance Therapy Following the Completion of an  
Initial Pulmonary Rehabilitation Program:  
A Systematic Review**

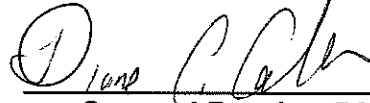
**By  
Paul D. Ossman**

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**Advisor and First Reader: Russ Harris**



**Second Reader: Diane C. Calleson**

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**Date**

**Background:** Pulmonary rehabilitation is associated with an improved health related quality (HRQL) of life and decreased hospital utilization over one year following rehabilitation, but not with decreased mortality or improved lung function. The sustainability of these improvements is controversial and the role of a pulmonary maintenance program or repeated pulmonary rehabilitation program is under investigation.

**Purpose:** To examine the evidence regarding the effect of additional pulmonary rehabilitation or maintenance therapy, following the completion of a conventional pulmonary rehabilitation program.

**Data Sources:** MEDLINE, the Cochrane Library, hand searching based on reviews and previous systematic reviews of pulmonary rehabilitation.

**Methods:** Randomized controlled trials of exercise maintenance programs following an initial pulmonary rehabilitation program of at least 6 weeks duration with at least a 1 year of follow-up; studies that used defined and validated measurement tools; studies that accounted for the reliability and validity of measurement tools as well as patient characteristics; and randomized controlled trials with health outcomes.

**Population:** Patients living with mild, moderate, or severe COPD

**Intervention:** Additional pulmonary rehabilitation following an initial course of pulmonary rehabilitation of at least 6 weeks.

**Control:** Short-term/acute pulmonary rehabilitation as defined by a period of time less than or equal to 6 weeks of pulmonary rehabilitation program.

**Outcomes:** HRQL, Mortality, Change in functional status (a six minute walk test, FEV1, etc.)

**Study Selection:** Of 496 citations identified, 79 articles were reviewed to yield 3 good to fair studies comparing exercise maintenance to usual care following an initial pulmonary rehabilitation program.

**Conclusion:** Current research is sparse, yet it suggests that continued exercise maintenance therapy is associated with modest improvements in exercise capacity, but not with any difference in lung function. Results were not conclusive as to a benefit in HRQL or dyspnea. Additionally, the selection and recruitment bias that exists within the studies regarding pulmonary rehabilitation weakens the generalizability of the data reported. Further research is needed to confirm the associations and further investigate the affects of HRQL and dyspnea following pulmonary rehabilitation and maintenance therapy.

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# **INTRODUCTION**

## **Burden of Disease**

Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease marked by chronic inflammation of the airways and lung parenchyma. This inflammation causes a limitation of airflow that is not fully reversible over time or with treatment.<sup>1</sup> Patients with advanced COPD experience dyspnea, exercise intolerance, generalized muscle weakness and dystrophy, cardiac impairments (eg, cor pulmonale), and nutritional deficiencies.<sup>2</sup>

According to estimates from the National Heart, Lung, and Blood Institute, the annual cost of COPD to the United States was \$23.9 billion in 1993<sup>3,4</sup> and has risen to \$32.1 billion in 2002.<sup>4</sup> Approximately 70% of this cost continues to be for inpatient hospitalization and emergency department care.<sup>3-5</sup> In 2000, COPD related emergency department visits reached 1.5 million and 119,000 adults died from COPD exacerbations.<sup>4,5</sup> COPD is the 4<sup>th</sup> leading cause of death and is projected to be the 3<sup>rd</sup> leading cause of death in 2020.<sup>4,5</sup>

## **Progression of Disease**

Due to the prolonged and variable asymptomatic phase of the disease and the varying levels of disease upon presentation, survival data are not conclusive; however, the long-term survival of patients living with symptomatic COPD, especially those who have been referred for pulmonary rehabilitation is poor. In a randomized trial of outpatient pulmonary rehabilitation, Ries, et. al. found the 6-year survival of the 119 patients with COPD was 61% and Gerardi et. al. found the 3-year survival following outpatient pulmonary rehabilitation was 80%.<sup>6,7</sup>

As COPD progresses, the forced expiratory volume in one second (FEV1) declines at an increasing rate. FEV1 is the primary physiological abnormality in COPD, yet the onset of the symptomatic phase does not occur until the FEV1 reaches approximately 50 percent of the predicted normal value. Additionally, the rate at which individual patients progress varies, as does how a patient will respond to therapy.<sup>1</sup> Disease severity and strength are also related to outcomes following pulmonary rehabilitation. Troosters et. al. demonstrated that weaker patients with less severe disease were more likely to respond to exercise therapy.<sup>8</sup> However, compared to patients experiencing a severe impairment in HRQL, patients with a moderate impairment in HRQL will have a more significant deterioration of benefits despite a more significant improvement following rehabilitation.<sup>9</sup> Personality traits may also affect the long term outcomes following pulmonary rehabilitation as they appear related to quality of life and coping mechanisms.<sup>10</sup>

### **Current Treatment**

The goals of current therapy are palliative and preventive in nature: symptom relief, improvement in physiological function, and limitation of exacerbations of the disease. Smoking cessation is a major goal of treatment as no other therapy reduces the rate of lung function decline as dramatically. Patients who quit smoking reduce their rate of lung-function decline by as much as 50%.<sup>11</sup> Providers often offer pneumococcal vaccination and annual influenza vaccination as a precautionary measure despite the lack of direct evidence that these vaccines improve outcomes.<sup>12</sup> Long and short acting inhaled

bronchodilators are the primary pharmaceutical intervention. They lessen symptoms, reduce exacerbations of disease, and improve the quality of life

An initial pulmonary rehabilitation program is recognized as an effective therapy in terms of short term-outcomes. Several studies confirm short-term benefits of an initial pulmonary rehabilitation program: increased exercise capacity, easing of dyspnea, and improvement in the health quality of life.<sup>1, 2, 13, 14, 15, 15, 16, 16-24</sup> While an initial pulmonary rehabilitation program may also reduces hospital utilization in the year following intervention,<sup>17, 22, 25-29</sup> Mortality does not appear to be affected by pulmonary rehabilitation.<sup>6, 15, 21, 22, 30-35</sup> The costs and benefits of pulmonary rehabilitation for COPD are discussed further in this paper in the discussion segment.

The long term benefits of a pulmonary rehabilitation program are questionable as the improvements gained following a pulmonary rehabilitation program tend to diminish over time; even in the studies that show some sustained improvement following a pulmonary rehabilitation program, the improvements still trend towards the null as time from pulmonary rehabilitation increases.<sup>6, 9, 22, 34, 36-38</sup> In this paper, I will investigate the role exercise maintenance plays in extending the benefits of an initial pulmonary rehabilitation program over time.

As COPD advances, using supplemental oxygen to maintain an oxygen saturation of at least 90 per-cent at all times has been shown to prolong survival.<sup>2, 39</sup> Lastly, lung volume reduction surgery plays a controversial role in patients with severe disease. Lung volume reduction surgery does not lead to a reduction in mortality; however, the National Emphysema Treatment Trial found that a

subgroup of patients had an overall improvement in health status. Conversely, mortality was increased in a subgroup of patients with severe physiological impairment (FEV1,  $\leq 20$  percent of the predicted normal value).<sup>40</sup>

Thus far, domiciliary oxygen therapy and smoking cessation have been the only therapies found to prolong survival and slow the decline of lung functioning respectively,<sup>2</sup> however, mortality and disease progression are only two of many outcomes that can measure a patient's health.

### **Current Role of Pulmonary Rehabilitation**

Pulmonary rehabilitation is similar to other exercise-based rehabilitation in that the participants benefit from therapy in three phases.<sup>41, 42</sup> Participants experience initial benefits during the formal program. Then, the initial gains made in the program are transferred into gains in physical performance. Lastly, these gains are maintained over time. Most studies investigate the outcomes during the initial stage. There is growing data on the first year following rehabilitation, but very few studies investigate the role of maintenance programs.

There is currently a debate over the sustainability of benefits received from pulmonary rehabilitation. Few studies investigate hospital usage after 12 months and fewer studies investigate the cost-effectiveness of rehab. Studies have shown a clinically and statically significant improvement at the end of rehabilitation, but the studies that follow patients for at least one year find a deterioration of functioning reverting back towards baseline over the year following the completion of pulmonary rehabilitation.<sup>6, 31, 36, 37, 43, 44</sup> The quality of these studies is problematic due to the number of drop outs and eligible patients

who chose not to participate.<sup>36, 37, 43, 44</sup> A more thorough discussion of these articles and the problems with patient compliance appears later in this paper.

Three randomized controlled trials studies with validated outcome measures indicate that benefits derived from pulmonary rehabilitation can persist over time (greater than 1 year after completion of therapy) without maintenance, but patients do begin to deteriorate by the end of follow-up.<sup>22, 34, 45</sup> These three studies also have problems with compliance and patient drop-out, but Griffiths et. al. use an intention to treat (ITT) analysis in an effort to account for poor compliance. Length and intensity of the program may contribute to the difference found in these three studies. Troosters et. al. and Guell et. al. studied patients who completed a course of rehabilitation that was longer than most programs (6 months rather than 6 to 8 weeks). Griffiths et. al. studied patients who participated in an intensive multidisciplinary program rather than exercise alone.

The findings of Lacasse et. al. support the association between better outcomes and a rehabilitation program lasting 6 months and longer. In a Cochrane Collaboration systematic review, Lacasse et. al. identified 7 quality studies of rehabilitation programs with a duration <6 months and 3 quality studies of rehabilitation programs with a duration  $\geq 6$  months. After meta-analysis, both groups of studies were associated with a clear benefit to patients, and the longer programs were associated with a greater cumulative benefit.<sup>18</sup> Lacasse et. al. declined to review the long term benefits of pulmonary rehabilitation as “too few investigators have examined the long-term benefits of rehabilitation.”<sup>18</sup>



As research continues on the lasting benefits of pulmonary rehabilitation and means to prolong the benefits following therapy, pulmonary rehabilitation continues to be recommended to patients. The American Thoracic Society recommends comprehensive pulmonary rehabilitation over standard medical management or educational management alone and recognize pulmonary rehabilitation provides benefits across several outcome areas: exercise ability, dyspnea, and improvement in health status.<sup>13</sup> The American Association of Chest Physicians (AACP) support pulmonary rehabilitation “for any patient with stable disease of the respiratory system and disabling symptoms.”<sup>21</sup> The ACCP recognizes lower extremity training as the best studied modality to improve exercise tolerance stating that this modality is supported by several well-designed, well-conducted, controlled trials. Upper extremity training and ventilatory muscle training are also recommended, but lack the rich evidence base of lower extremity training.<sup>15, 21</sup>

## **Methods**

### **Search Strategy and Study Selection**

I searched MEDLINE, The Cochrane Library, and hand searched relevant citations from previous systematic reviews of pulmonary rehabilitation for relevant studies to the key question: for patients living with COPD, what are the effects of a program of exercise maintenance following an initial pulmonary rehabilitation program? I used Medical Subject Headings (MeSH) search terms

as well as key words where appropriate.\* I limited the search to “English language,” and “human.” Excluding hand-searches my literature search found 496 citations, of which I reviewed 79 articles (See Table 1).

I first retrieved the 496 abstracts of any article whose title suggested the article may contain data on pulmonary rehabilitation and COPD. The great majority of these abstracts were available through MEDLINE and those not available on MEDLINE were reviewed from the original article. I excluded only articles that clearly did not focus upon either pulmonary rehabilitation or COPD. I again excluded articles that clearly did not focus on an exercise maintenance program following pulmonary rehabilitation.

**Table 1:** Search Strategy

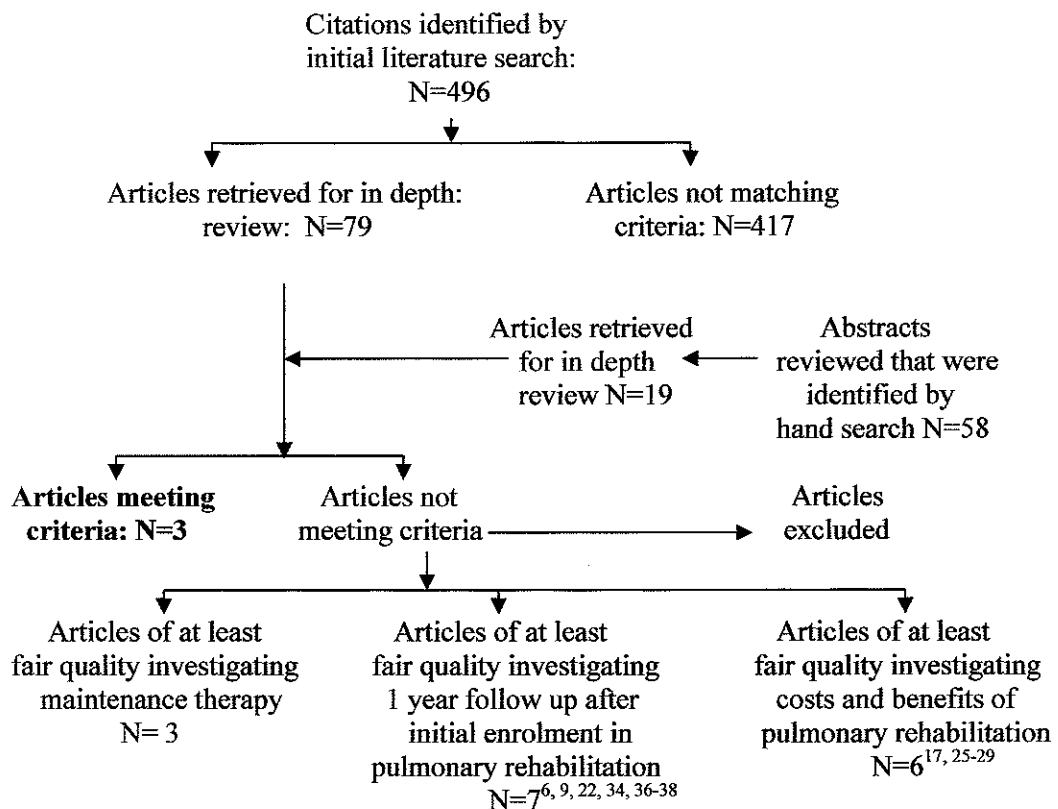
Key Question	Search Strategy	Articles Identified for abstract review/Articles Identified for in depth review
What are the effects of additional pulmonary rehabilitation following an initial 6 week course of pulmonary rehabilitation	COPD (MeSH and text word)+Rehabilitation (text word and subheading) + Quality of Life(MeSH and text word)	329 / 50
	COPD (MeSH and text word)+Rehabilitation (text word and subheading) + Long-term (all fields) (excluding repeats from above search)	132 / 9
	COPD (MeSH and text word)+Rehabilitation (text word and subheading) + Maintenance(MeSH and text word)	26 / 11
	COPD (MeSH and text word)+Rehabilitation (text word and subheading) +Postrehabilitation (all fields)	8 / 1
	Hand Searched	58 / 19

\* (("chronic obstructive pulmonary disease"[Text Word] OR "pulmonary disease, chronic obstructive"[MeSH Terms] OR copd[Text Word]) AND ("rehabilitation"[Subheading] OR "rehabilitation"[MeSH Terms] OR rehabilitation[Text Word]) AND (postrehabilitation [All Fields] OR long-term[All Fields] OR ("quality of life"[MeSH Terms] OR Quality Of Life[Text Word]) OR ("maintenance"[MeSH Terms] OR maintenance[Text Word])) AND English[Lang] AND "humans"[MeSH Terms])

Upon retrieving and reviewing the 79 articles that remained, I again excluded articles that clearly did not focus on an exercise maintenance program following pulmonary, as well as excluding articles that lacked a 1 year follow-up post beginning the initial pulmonary rehabilitation program. Additionally, randomized controlled trials were preferred and studies without an adequate control group were excluded. Studies that did not use validated measures of outcomes were excluded as were studies that did not use an initial rehabilitation program of at least 6 weeks duration. Studies were also excluded if baseline patient characteristics were not reported or if the overall quality of the article was poor. (See Table 1 for search strategies and process).

I kept aside articles of at least fair quality that followed up on patients at least one year after enrolment in an initial pulmonary rehabilitation program, articles that investigated the costs and benefits of pulmonary rehabilitation for at least one year after enrolment in an initial pulmonary rehabilitation program, and any study investigating maintenance therapy following a pulmonary rehabilitation program (See Figure 1).

FIGURE 1: Literature Review



### Quality assessment

I used a structured data abstraction to ensure consistency in appraisal of each article. I abstracted the following data from each article: characteristics and size of patient group; recruitment strategy; patient adherence and drop-outs; length of rehabilitation; length of follow-up, inclusion criteria, exclusion criteria, and outcomes measures. I assessed the external and internal validity of the studies and evaluated each article for overall quality.

**Table 3:** Evidence Table for Eligible Articles

Study	Quality	Patient age	Severity	Groups (patients)
Berry et. al. <sup>46</sup>	Fair	Control mean age = 66.9. Treatment mean age = 68.4	Moderate to severe	Control: 3 month exercise program = 70 began and 56 completed.  Treatment: 3 month exercise program followed by an additional 15 month exercise program = 70 began and 62 completed treatment.
Ries et. al. <sup>31</sup>	Good	67.1 $\pm$ 8.2	Moderate to severe	Control: 8 weeks pulmonary rehabilitation and referral back to PCP = 73 of 81 received standard care  Treatment: 8 weeks pulmonary rehabilitation followed by self directed, at-home EM with weekly telephone calls and monthly supervised reinforcement sessions for 24 months = 75 of 83 received intervention
Weiner et. al. <sup>47</sup>	Fair	Mean age of Control = 64.9 Mean age of Treatment = 66.3	Moderate to severe	3 month training with inspiratory muscle trainer = all 38  Control: additional 12 months of low-load training at home = 16 began and 9 finished.  Treatment: additional 12 months training with inspiratory muscle trainer = 16 patients began, 12 finished.

**Table 3:** Evidence Table for Eligible Articles

Study	Recruitment and Enrolment	Adherence and Withdrawal
Berry et. al. <sup>46</sup>	Before randomization, participants must have completed 3 screening visits (207 of 775) and completed at least 60% of the exercise sessions of a 3 month exercise program (140 of 775).	<p>Of the 70 control participants, 56 completed the trial. Of the 70 treatment participants, 62 completed the trail.</p> <p>Of all the measured outcomes in the treatment group, the 6 minute walk test was the only outcome affected by compliance when broken down into tertiles (0-44%; 45-82%; 83-97%)</p>
Ries et. al. <sup>31</sup>	Patients must have graduated from pulmonary rehabilitation to be eligible. For the enrolment period of the study, 340 patients began the pulmonary rehabilitation program and 190 completed the pulmonary rehabilitation program. 172 patients were considered eligible, and all eligible patients were randomized.	After randomization, 6 patients (3 from each group) dropped out before starting treatment and 2 patients (1 from each group) withdrew due to lung volume reduction surgery. An additional 1 patient from the treatment group and 2 patients from the control group withdrew before the 6 month assessment. The remaining group was assessed for outcomes. Of the remaining 82 patients in the treatment group, 7 patients died in first year, 10 died in the second year, and 0 patients dropped out. Of the remaining 81 patients in the control group, 6 patients died in first year, 10 died in the second year, and 0 patients dropped out.
Weiner et. al. <sup>47</sup>	Consecutive enrollment of pts. meeting eligibility requirements from chosen community (65% of those recruited were eligible). Eligibility requirements excluded patients with poor compliance (see inclusion/exclusion criteria).	4 week run-in period with pts.' regular treatment. Pts. with poor compliance were excluded. Randomization to control or experimental occurred after initial 3 month pulmonary rehabilitation program (6 patients dropped out). From the 32 patients randomized, 11 dropped out: (4 experimental and 7 control).

**Table 3:** Evidence Table for Eligible Articles

Study	Inclusion Criteria/ Exclusion Criteria	Comments
Berry et. al. <sup>46</sup>	FEV1/FVC $\leq 70\%$ ; reported difficulty in ADL secondary to dyspnea; had not participated in a pulmonary rehabilitation program in the last 6 months; FEV1 $> 20\%$ of predicted; no severe cardiovascular or peripheral vascular disease; not undergoing treatment for cancer; no uncontrolled diabetes or HTN; no plans to move away from the area within 15 months of beginning the study.	No disease specific HRQL or ADL measurement tool used.  No follow-up for the treatment group after long-term pulmonary rehabilitation ended.  Subgroup analysis of compliance by tertile indicates compliance was significantly associated with an improvement in 6-minute walk distance only.
Ries et. al. <sup>31</sup>	Clinical diagnosis of COPD confirmed by history, physical examination, pulmonary function tests, and chest roentgenograms; chronic symptoms and perceived disability from disease; stable on an acceptable medical regimen under the care of a primary care physician; no other significant medical or psychiatric conditions that would interfere with full participation in the program; commitment to abstain from smoking.	At one year post-maintenance, subjects in both groups had returned to levels similar to baseline. There was no difference in survival over two years of follow-up between the two groups.
Weiner et. al. <sup>47</sup>	For recruitment: FEV1 $< 50\%$ predicted or FEV1/FVC $\leq 70\%$ ; and diagnosed with COPD according to ATS criteria; no cardiac disease, no history of poor compliance, not requiring supplemental oxygen, no carbon dioxide retention.	How the community was chosen and how patients were recruited is not published. The number of pts. recruited and pts. eligible is not published. All pts. new to pulmonary rehabilitation.

**Table 4:** Outcome Measures

Study	Outcome Measures
Berry et. al. <sup>46</sup>	<p><b>Self Reported Disability:</b> Treatment group reported 12% less disability than the control group at 18 m</p> <p><b>6MW:</b> Treatment group walked 100 feet further at 18 m P= 0.03</p> <p><b>Dyspnea:</b> Not measured</p> <p><b>FEV1/FVC:</b> No significant difference between groups at 18 m.</p>
Ries et. al. <sup>31</sup>	<p><b>HRQL:</b> Significant decline (CRQ, Rand-36) at 14m in both groups; no significant change (QWB) at 14m in both groups; significantly better maintained (10PHS) in the treatment group at 14 m.</p> <p><b>6MW:</b> Significantly better maintained in the treatment group at 14 m</p> <p><b>Dyspnea:</b> Significant decline in PB at 14 m in both groups</p> <p><b>FEV1/FVC:</b> Significant decline at 14 m in both groups.</p> <p><b>Maximum Treadmill Exercise:</b> Significantly better maintained in the treatment group at 14m.</p> <p><b>Health Care Usage:</b> Overall reduction in hospital utilization in the treatment group at 26m.</p>
Weiner et. al. <sup>47</sup>	<p><b>HRQL:</b> Not measured</p> <p><b>6MW:</b> Training group gained small benefit through 15m; control group declined toward baseline from 3m to 15m.</p> <p><b>Dyspnea:</b> Training group gained small benefit through 15m; control worsened toward baseline from 3m to 15m.</p> <p><b>FEV1/FVC:</b> No significant change in either group</p> <p><b>Inspiratory muscle strength:</b> Training group gained small benefit; control declined toward baseline from 3m to 15m.</p>

HRQL: Health Related Quality of Life; 6MW: 6 minute walk distance; CRQ: Chronic Respiratory Questionnaire; Rand-36: Rand 36-Item Health Survey; QWB: Quality of Well-Being Scale; 10PHS: 10-point overall health scale; PB: Perceived Breathlessness; PI: maximum mouth inspiratory pressure. All time measures are measured from the beginning of the initial pulmonary therapy.



**Table 5:** Notable articles of interest that were excluded: Articles of at least fair quality investigating maintenance therapy following an initial pulmonary rehabilitation program and articles of interest comparing length of pulmonary rehabilitation programs.

Study	Main reason for exclusion	Additional weakness	Result
Brooks <sup>36</sup>	Maintenance program not an exercise program. No suitable control – compared two post-rehabilitation programs	Retention rates were poor in both groups: of the 109 eligibles, 24 dropped out after initial evaluation, and 44 dropped out over the course of the study (38% of eligibles remained at the end of the study).	Clear deterioration of functional exercise capacity and HRQL in all groups without major differences between groups
Elliott <sup>43</sup>	No suitable control – compared hospital to home to community based programs	Retention rates were poor: 37% of all participants in all groups remained at 1 year.	Long-term outcomes could not be measured and the effect of maintenance could not be calculated due to significant drop-out.
Foglio <sup>37, 48</sup>	Investigated a repeat pulmonary rehabilitation program rather than maintenance.	Recruitment and enrolment was limited to the compliant participants of an earlier pulmonary rehabilitation program. Drop-out rate was significant	Participants who repeated a pulmonary rehabilitation program at 1 year after completion on an initial pulmonary rehabilitation program achieved immediate improvements in HRQL and decreased hospitalizations. These benefits diminish in the long-term with the exception that yearly exacerbations were reduced in the long-term.

Articles were considered notable if they were often cited by guidelines, position statements, and the current literature concerning COPD rehabilitation.

**Table 5:** Notable articles of interest that were excluded: Articles of at least fair quality investigating maintenance therapy following an initial pulmonary rehabilitation program and articles of interest comparing length of pulmonary rehabilitation programs.

Grosbois <sup>49</sup>	Non-randomized	No reporting of drop-outs during initial pulmonary rehabilitation program. Patients self selected their maintenance program: EM twice weekly, EM once weekly, EM at home, no EM.	EM is associated with less diminishment of improvement following pulmonary rehabilitation over 18 months.
Green <sup>50</sup>	Compared 4 weeks of a pulmonary rehabilitation program to 7 weeks of pulmonary rehabilitation; insufficient follow-up	Differences existed between groups in baseline shuttle walk test and HRQL.	7 weeks was superior to 4 weeks in terms of immediate benefit
Rossi <sup>51</sup>	Observational prospective trial comparing 10 sessions of a pulmonary rehabilitation program to 20 sessions of pulmonary rehabilitation; insufficient follow-up.	All patients enrolled in a 20 session pulmonary rehabilitation program. Measurements taken after 10 sessions and compared to measurements at 20 weeks. It is unclear if the outcomes were due to the additional sessions of pulmonary rehabilitation or were latent effects from the first 10 sessions.	Compared to measurements taken after 10 sessions, the measurements taken after 20 sessions showed a statistically greater increase in 6 minute walk distance and HRQL from baseline.

Articles were considered notable if they were often cited by guidelines, position statements, and the current literature concerning COPD rehabilitation.

## **Results:**

The 3 studies of good to fair quality all investigate patients with moderate to severe diseases.<sup>31, 46, 47</sup> The mean age of patients for all three studies range from 66.3<sup>47</sup> to 68.4<sup>46</sup>. The patients in all three studies first must have completed an initial rehabilitation program to be included in the final analysis. Initial rehabilitation programs ranged from 8 weeks<sup>31</sup> to 3 months.<sup>46, 47</sup> The treatment groups in all three studies consisted of patients who enrolled in a year long exercise maintenance program following initial rehabilitation.

All three studies report significant attrition of patients before randomization, either in selection or during the initial pulmonary rehabilitation program. Berry et. al. report, of the 775 patients beginning the initial pulmonary rehabilitation program, 207 patients completed the program (73% attrition rate). Ries et. al. report, of the 340 patients beginning the initial pulmonary rehabilitation program, 190 patients completed the program (44% attrition rate). Weiner et. al. report, of all the patients recruited, only 64% were eligible, and of the 38 patients eligible who began the initial pulmonary rehabilitation program, 32 patients completed the program (84% attrition rate).

A significant number of patients in all three studies dropped-out or died during the year of maintenance therapy. Berry et. al. report, of the 140 patients randomized to maintenance therapy or conventional care, 118 patients completed the program (84% retention rate). Ries et. al. report, of the 164 patients randomized to maintenance therapy or conventional care, 131 patients completed the program (78% retention rate). Weiner et. al. report, of the 32 patients

randomized to maintenance therapy or low-load home-based training, 21 patients completed the program (65% retention rate).

The three studies share two common outcome measures: 6 minute walk distance (6MW) as a measure of exercise tolerance and FEV1/FVC as a measurement of lung function. Weiner et. al do not evaluate health quality of life (HRQL), quality of life (QOL), or activities of daily living. Berry et. al. evaluate self reported physical disability as measured by the activities of daily living as captured by the Fitness Arthritis and Seniors Trial functional performance inventory. Ries et. al. measure HRQL through different instruments: Chronic Respiratory Questionnaire (CRQ), Rand 36-Item Health Survey (Rand-36), Quality of Well-Being Scale (QWB), and 10-point overall health scale (10PHS). Of the tools used, the CRQ is the only disease specific tool, and the 10PHS is the only tool not independently validated. Berry et.al. do not measure dyspnea; Reis et. al. measure dyspnea using the UCSD Shortness of Breath Questionnaire and Weiner et. al. used the Borg scale. Reis also measure health care usage and maximal treadmill workload as estimated in terms of metabolic equivalents (METS) based on speed and grade. Weiner et. al. also measure maximum mouth inspiratory pressure. These tools and measures have been independently validated.

Exercise capacity, as measured by the 6MW and the maximum treadmill exercise, was consistently higher in the treatment groups at the end of maintenance when compared to the control groups. Weiner et. al. and Berry et. al. demonstrate a continued improvement in the treatment group as compared to a

steady decline in the control group. Ries et. al. report declines in both the treatment and the control groups; however, the treatment maintained the benefits from initial pulmonary rehabilitation significantly better.

HRQL, activities of daily living, and dyspnea differed by study as well as measurement tool. Using the Fitness Arthritis and Seniors Trial functional performance inventory, Berry et. al. demonstrate maintenance therapy was associated with 12% less disability. Using the Borg Dyspnea scale, Weiner et. al. demonstrate that from 3 months to 15 months after initiation of an initial pulmonary rehabilitation program, the training group continued to see small improvements (decrease in their Borg score) while the control group began and continued to worsen toward baseline. This difference became statistically significant from 9 months through 15 months. Reis et. al. use three different tools to measure HRQL and only the 10PHS illustrated an association of improvement with maintenance therapy at 12 months following the completion of an initial pulmonary rehabilitation program. It is important to note that the 10PHS has not been independently validated. All patients significantly declined in their CRQ and Rand-36 scores with no difference between groups. There was no significant change or difference in QWB in either group.

No study was able to illustrate a difference between groups by comparing the FEV1/FVC. Ries et. al. demonstrate an overall reduction in healthcare utilization associated with treatment. This reduction was evident over the 1 year of therapy and continued to be significant at 2 years.

## **Discussion**

The largest barrier to a sound recommendation is the lack of evidence is both quality and quantity. Exercise capacity, as measured by the 6MW and the maximum treadmill exercise, was consistently higher in the treatment groups at the end of maintenance when compared to the control groups, but this agreement is only within three studies of good to fair quality. HRQL, activities of daily living, and dyspnea differed by study as well as measurement tool. The two tools illustrating the greatest benefits are the Fitness Arthritis and Seniors Trial functional performance inventory<sup>46</sup> and the 10PHS<sup>31</sup>. Neither tool is disease specific and the former is not a standard measurement tool while the latter has not been validated externally. Only one study used disease specific HRQL tools and Reis et. al. could not demonstrate a difference using this tool. As is the case with previous rehabilitation studies, no study on maintenance programs were able to illustrate a difference between groups by comparing the FEV1/FVC

The notable studies that did not meet the eligibility requirements (see Table 5) lack the rigor to be conclusive, but the trend of these studies is consistent with the findings of the three articles meeting criteria. Retention rates, recruitment, and enrollment are all problematic. Outcomes are varied from no effect to a modest benefit associated with maintenance. In the following discussion, HRQL as an outcome measure and the tools used to measure HRQL; the costs and benefits associated with pulmonary rehabilitation; and patient enrolment, recruitment, and compliance.

### **HRQL and Pulmonary Rehabilitation**

Recently, HRQL has been used to demonstrate the effectiveness of pulmonary rehabilitation to improve the outcomes of patients living with COPD. In theory, measuring changes in a patient's HRQL aids in understanding the intervention's effect on the patient's health; however, demonstrating a clear causal relationship is often difficult in practice. Pulmonary rehabilitation is associated with improved responses to HRQL questionnaires, yet a direct causal relationship between the pulmonary rehabilitation and improved health remains complicated with additional and unintended inputs that pulmonary rehabilitation may provide to patients: psychological benefits of the social aspects of pulmonary rehabilitation, more realistic expectations of the limitations secondary to the disease, coping skills. Secondly, the individual tools used to measure HRQL and how the investigators used these tools affect the validity of the measurement obtained. Lastly, an improvement in HRQL is often used as an outcome measure following pulmonary rehabilitation, yet as an outcome measure, HRQL lacks the strength it would have if a direct causal relationship could be proven between the therapy and the outcome.

### **HRQL as an Outcome Measure for Pulmonary Rehabilitation.**

"Health" represents multiple variables: symptoms, the degree of disability or of ability to function, the degree of disease or to which one is free of disease. Each variable carries with it multiple connotations and "because of this multidimensionality, there is an almost infinite number of health states, all with differing qualities, and all quite independent of longevity."<sup>52</sup> We begin to tease

out the effect of an intervention on a person's health by combining the measurement a person's QOL and HRQL as it changes over the course of an intervention with more traditional outcomes such as the rate of the progress of disease, mortality, change in functional status as measured by a six minute walk test or FEV1/FVC. This approach is different from limiting our observations only to how that intervention affects lifespan or other biological/physiological markers. Attempting to measure health involves moving away from provider-specific outcomes to outcome measures that are patient-specific. Provider-specific, physiologic outcomes do not reflect patient-specific outcomes. Physiologic measures such as FEV1/FVC do not correlate with the perceptions of patients living with COPD. Physiologic measures also may fail to detect important changes in health status.<sup>53</sup>

Current research increasingly uses HRQL as an outcome to evaluate pulmonary rehabilitation. pulmonary rehabilitation does not change affect mortality; however, pulmonary rehabilitation is effective in improving exercise capacity and HRQL in COPD patients.<sup>45</sup> The strength of HRQL assessment is that it is patient-centered and echoes the direction that health care has been moving – from a disease-oriented approach to a patient-oriented approach.<sup>54</sup> Testa and Simonson state that while “the objective dimension is important in defining a patient's degree of health, the patient's subjective perceptions and expectations translate that objective assessment into the actual quality of life experienced.”<sup>54</sup>



However, this strength of HRQL as an outcome measure is also a weakness of the tool. Testa and Simonson admit the difficulty in measuring health strictly from a QOL standpoint “Since expectations regarding health and the ability to cope with limitations and disability can greatly affect a person’s perception of health and satisfaction with life, two people with the same health status may have very different qualities of life.”<sup>52</sup> We should not conflate health and HRQL as the two clearly represent different aspects of a patient’s existence; however, a patient’s perception does not always discriminate such subtleties.

Both the intervention of pulmonary rehabilitation and the measurement of HRQL are complex in their own right, and using the latter as an outcome measure of the former proves difficult. Even so, the complexity of the measure may be perfected suited for PR if the measure is obtained reliably. “Successful pulmonary rehabilitation requires patients to incorporate a complex array of changes in behavior (e.g., exercise, compliance with medications/oxygen, breathing retraining methods, lifestyle changes).”<sup>31</sup> Additionally, the HRQL reflects “a person’s own satisfaction or happiness with the life in the domains he or she considers important.”<sup>54</sup> In these complexities lies interconnectedness. HRQL may be more sensitive to detect the effects of pulmonary rehabilitation that teaches and trains patients to be successful in many areas in which the HRQL measurement tool is sensitive such as coping mechanisms and improved functioning.

### **Disease Specific HRQL Tools to Increase Specificity**

Wilson and Cleary state the “the concept of quality of life is distinct from health, though related to it,”<sup>55</sup> and by measuring HRQL rather than general QOL, we can observe a more accurate relationship. HRQL allows a clearer investigation of the aspects of life most affected by health: “dimensions of physical functioning, social functioning, role functioning, mental health, and general health perceptions.”<sup>55</sup>

Additionally, COPD patients are a disease-specific population and the PR offered to these patients is fairly specific for those living with COPD. Such homogeneity, from a disease standpoint, allows the use of a disease-specific HRQL instrument. Given this population, one sacrifices very little with respect to generalizability to a population other than COPD patients because such generalizability is not a primary goal. Thus, a disease specific tool allows for a higher content validity.

The studies of pulmonary rehabilitation using disease specific HRQL tools are relative since they are not generalizable to other conditions. The data collected using COPD-specific HRQL cannot be compared to patients with another disease. This lack of standard application limits the use of the research when the investigators only use a disease-specific HRQL tool.<sup>56</sup> For example, studies that employ only the CRQ or the St. George’s Respiratory Questionnaire (SGRQ) to assess HRQL as an outcome measure of pulmonary rehabilitation could not be used to compare pulmonary rehab to cardiac rehab. Even with this limitation, using only a disease specific tool has benefits. Fewer questions spare

the patients the burden of filling out multiple disease-specific batteries or a combination of general and disease-specific assessments. Such a reduction in burden may increase the precision and accuracy of the single instrument.<sup>54</sup> With COPD and pulmonary rehabilitation, obtaining immediate results favor a single, disease-specific tool; however, for future research and secondary analysis, collecting data with a general assessment may prove useful.

### **Measurement of HRQL as Reported in the Literature**

In a systematic review of the literature on pulmonary rehabilitation, Sin et. al.<sup>2</sup> and Lacasse et. al.<sup>18</sup> illustrate that pulmonary rehabilitation improves HRQL. Both studies use many of the same articles and all 19 studies Sin et. al. selected for the systematic review used at least either the CRQ and/or the SGRQ to assess HRQL. The SGRQ (zero indicating no health impairment and 100 representing maximum impairment) consists of 50 items with 76 weighted responses and three component scores: symptoms, activities and impacts (psychosocial dysfunction). It is sensitive to changes in health status with treatment for COPD, and it is a valid and reliable measure of health status in patients with COPD.<sup>23</sup> The CRQ includes 20 items in four domains: dyspnea (five items), fatigue (four items), emotional function (seven items), and mastery (four items), each item being graded on a seven-point scale.<sup>45</sup> Some studies also collected data using additional generalizable HRQL questionnaires as well as depression assessment: QWB, EADL, HAD. All assessment tools selected for comparison between the 19 studies have been previously validated.<sup>54</sup>

All 19 studies seem to use the tools within the populations for which they were intended as the clinical trials were investigating patients with chronic, fixed airway obstruction. The CRQ and SGRQ are both designed for such a population. However, Mishoe and Maclean propose that intended use goes beyond the specific population and even intended use is not sufficient by itself. In a disease specific questionnaire, “validity is relative; therefore, clinical trial protocols should incorporate the rationale and instructions for HRQL assessment to assure validity within the research study.”<sup>54</sup> Mishoe and Maclean go on to suggest that “clinical protocols should explain why, how, and when the HRQL assessments will be completed, provide justification for instruments selected for use and described how these data will be analyzed,” as well as the burden placed on patients in terms of time spent waiting to answer and answering the questionnaire.<sup>54</sup>

While most of the 19 studies state their rationale and a brief explanation of how the assessment was conducted, the variation in details are great. Some studies provide no details of the manner in which the questionnaires were administered, and other studies lacked information regarding the language and contained no rationale. Some studies made an attempt to discuss the timing of assessment, but, quite often, these data were quite limited. For example Ries et. al. provide information on the rationale and the fact that the questionnaire was given at different times, yet the timing was not discussed. “The CRQ was administered by an interviewer. This disease-specific quality of life instrument evaluates four domains: dyspnea, fatigue, emotional function, and mastery.

Patients were asked to rate overall health status on a 10-point scale ranging from 0 (dead) to 10 (excellent). In addition, this was obtained routinely by rehabilitation staff at the first contact (to assess the effect of screening).”<sup>31</sup>

While data on how the researchers conducted the questionnaire were available in some studies, this information was often at the expense of the rationale. “Patients were assessed using a standard 6-min walk, and completed the SGRQ; both tests were supervised by a blinded observer who subsequently repeated these assessments at 12 weeks and 24 weeks. Patients were then randomized to either the rehabilitation program or to routine outpatient attendance at 3-month intervals. Randomization was in blocks of 10, using random numbers.”<sup>24</sup> A small minority of the studies explained their methods in using a questionnaire.<sup>33, 57, 58</sup>

Larson et. al. explain, “The Chronic Respiratory Questionnaire (CRQ) was used to measure the intensity of dyspnea and fatigue experienced by patients on a daily basis. Guyatt and colleagues recommended that subjects be informed of their most recent answer on each item before giving their current answer. For the purposes of this study we blinded patients to their responses on previous visits. This was done to minimize the bias to report improvement, because most patients anticipate benefits from exercise training. The reliability of this modified technique was supported by acceptable test–retest reliability when the instrument was administered twice to patients with COPD, with a 1-wk interval between administrations. The test–retest reliability coefficients were as follows: CRQ Dyspnea,  $r = 0.73$ ,  $df = 48$ ; CRQ Fatigue,  $r = 0.69$ ,  $df = 68$  (our unpublished data,

1998). The CRQ has been widely used in surveys of patients with COPD and its validity has been established.”<sup>57</sup>

Larson et. al.<sup>57</sup> and Stulbarg et. al.<sup>58</sup> discuss many of Mishoe and Maclean’s suggestions as well as the use of blinding patients’ previous responses versus supplying the patients with their previous responses. Such blinding may reduce recall bias in that patients may want to be better after a rehab program, yet some studies suggest that by supplying patients with their previous responses, the responsiveness of the assessment is improved. Interestingly, all these studies had similar results. None of the studies included information that would be useful in determining the burden placed on patients.

#### **Assessing the Relationship between Pulmonary Rehabilitation, Exercise Maintenance and HRQL**

The studies reviewed show the same directional relationship in the improvement of HRQL associated with both pulmonary rehabilitation and exercise maintenance. This finding is consistent with the body of literature available concerning pulmonary rehabilitation and COPD. Although it may be tempting to articulate a causal relationship, data are insufficient to claim that pulmonary rehabilitation caused the improvement. First, the strength of the relationship is weakened by the fact that only 2 of the 19 studies investigated by Sin et. al. illustrate rigor in their attention to the delivery of the HRQL assessments.<sup>57, 58</sup> However, this aspect of delivery is a minor point, not because of the overall quality of the studies, but because more important factors challenge causal relationships derived by HRQL assessment.

As Wilson and Cleary demonstrate that there is an association between the HRQL measured and the clinical measures of disease. The association between HRQL and general perceptions of health is important because general perceptions of health are strong predictors of mortality.<sup>55, 59</sup> However an association is not sufficient to prove causality; additionally, predictions can be made using associations but, likewise, prediction is not sufficient to prove causality. Further, all studies failed to show a change in mortality, which raises the suspicion that rather than an organic change of true functioning, patients may be changing “their expectations and aspirations as circumstances change.”<sup>55</sup>

Adding to the skepticism, some studies “suggest that assessment of HRQL can lead to improvements in HRQL.”<sup>55</sup> The change in expectation and the psychological component that a patient in PR receives from receiving treatment leads to the introduction of a significant source of bias. It is extremely difficult to devise a plan where patients would engage in placebo pulmonary rehabilitation and be blinded. Additionally, the role of interacting with others and engaging in introspection about their disease is unknown. Some of this bias is controlled by offering the control patients education and the fact that all participants answer the questionnaire, but the effect of the rehab itself is difficult to isolate.

We have yet to resolve the consequence of the introduction of bias and confounding. “There has been relatively little research to date that either explicitly conceptualizes the relationships of clinical variables to measures of HRQL or attempts to determine the intervening variables that mediate these effects.”<sup>55</sup> HRQL as an outcome measure is not unlike many measures in that the

effectiveness remains difficult to measure and one must remember that HRQL is not a sole measure. Taken with other measures, HRQL remains a useful tool in assessing patient-related outcomes in the face of provider-specific physiological measures. Finally associations are not useless; some studies demonstrate “measures of HRQL can be as sensitive to clinically important changes as traditional clinical variables and can detect important differences not assessed by such endpoints.”<sup>55</sup> Even if HRQL is a surrogate for other unmeasured variables, HRQL challenges us to seek those variables in evaluating patient care from both the providers’ and the patients’ perspective while being a valuable predictor of other hard outcomes.

#### **Cost-Effectiveness of PR**

In addition to determining the HRQL, as complete of a picture of the benefits derived from pulmonary rehabilitation is needed to determine the true benefit of rehabilitation. This benefit can then be compared with the cost of therapy. While the results of cost-benefit analyses and studies of hospital utilization show promising results for pulmonary rehabilitation as a life enhancing and cost reducing (or at least a cost effective) treatment, the long term effects must be studied further. More studies with greater numbers of participants over longer periods of time are needed to better evaluate the cost-effectiveness of pulmonary rehab. Especially important is whether the cost savings or cost neutrality of pulmonary rehabilitation is sustainable or if the programs merely postponed the inevitable costs of the disease. If sustainable cost savings are not



possible, HRQL improvements must be weighed against the costs in order to create guidelines for the most efficient use of resources

As stated in the introduction, COPD, while treatable, is not curable and ultimately life ending. Additionally, as discussed in the introduction, the literature agrees that pulmonary rehabilitation for COPD is efficacious in improving health related quality of life for some period of time. Recent studies suggest that pulmonary rehabilitation may be a cost effective treatment for those who live with COPD.<sup>17, 25-29</sup> These studies investigate the costs and benefits of pulmonary rehabilitation as well as hospital utilization. While the results are favorable, the studies are not of the highest quality and the effects beyond one year must be studied further.

Golmohammadi et. al. used a pre-post comparison to investigate the cost-effectiveness of a community-based pulmonary rehabilitation program for COPD patients with mild, moderate, and severe disease.<sup>25</sup> The investigators studied 210 patients living with COPD one year before and after completion of rehabilitation and compared the direct costs (in Canadian dollars) and disease-specific quality of life to the data obtained on 592 COPD patients from the same region who did not participate in the rehabilitation program. The average reduction of total costs before and after the program was \$34,367 per 100 person-years attributed to an associated decreased health service utilization, reduced direct costs and improved health status of COPD patients.

Hui et. al. and California Pulmonary Rehabilitation Collaborative Group conducted a similar study. Hui et. al. preformed a similar pre-post comparison as

part of a prospective longitudinal study investigating the efficacy of a simple outpatient-based pulmonary rehabilitation program in improving health outcome and hospital utilization in patients with COPD. The investigators studied patients from the outpatient physiotherapy department at a district general hospital who completed of a simple pulmonary rehabilitation. Hui et. al. found that in the 12 months following completion of program, hospitalization and length of stay were reduced compared to prior to starting the program (preprogram, 7.4 days; postprogram, 3.3 days;  $p < 0.005$ ).<sup>17</sup>

The California Pulmonary Rehabilitation Collaborative Group preformed a similar pre-post comparison to evaluate pulmonary rehabilitation as practiced in the general California medical community.<sup>28</sup> Dyspnea, HRQL, and reducing the use of healthcare resources were studied by investigating the common clinical health outcome data on consecutive patients at 10 established pulmonary rehabilitation programs over 2 years. Nine of the ten centers agreed to participate and of the 647 patients that met prespecified inclusion criteria, 521 completed the rehabilitation program and both the pre- and the postprogram assessment. After rehabilitation, there were significant reductions in all measures of healthcare utilization as well as improvement in HRQL over 18 months. The high completion rate (relative to other studies of pulmonary rehabilitation) highlights the recruitment and enrolment were based on patients who were referred to a rehabilitation program, chose to attend, and could afford to attend. This bias affects the generalizability of this study.

For these three studies, the absence of a control group, it is difficult to ascertain the effect of increased monitoring and access to care upon the outcomes. Additionally, the enrolment for both studies was done through referral rather than serial enrolment or active recruiting. The design of these studies is not as strong as a randomized controlled trial, and while the results suggest that pulmonary rehabilitation is cost-effective, one may reason that the health care expenses may be shifted to later years. However, since pulmonary rehabilitation is not associated with a change in survival, one may also reason that there is no shifting. Rather, patients may live in a more healthy state for the same number of years.

Griffiths et. al. used an RCT to assess the effect of outpatient pulmonary rehabilitation on use of health care and patients' wellbeing over one year and report pulmonary rehabilitation appears to be an effective intervention in patients living with COPD.<sup>26</sup> The investigators studied 200 patients who were randomly assigned a 6-week multidisciplinary rehabilitation program or standard medical management. Data was gathered on the use of health services and assessed via an ITT analysis. The ITT analysis is a major strength of this study and is relatively unique in that the results are based on the patients that began rehabilitation rather than on those who completed the program. There was no difference found between the rehabilitation and control groups with regard to the number of patients admitted to the hospital. However, the average number of days these patients spent in hospital differed significantly: 10.4 days vs. 21.0 days,  $p=0.022$ ).

Rea et. al.<sup>27</sup> compare the effect of a multi-disciplinary disease management program with conventional care, on hospital admissions and quality

of life. The investigators studied one hundred and thirty-five COPD patients that were recruited and enrolled based on hospital admission data and general practice records. The randomization for this study was conducted by randomizing entire general practices to either conventional care or a disease management program. Admission data was then compared for 12 months prior to and during the trial. In the year following rehabilitation, the mean hospital bed days per patient per year were reduced from 2.8 to 1.1 in the rehabilitation group, and increased from 3.5 to 4.0 in the conventional group.

While this study uses a pre-post comparison, there is also a randomized arm to which the treated group can be compared. Another strength of this study was patient retention. Randomization occurred before eligibility was determined and of the 99 patients randomized and eligible for rehabilitation, 71 completed the 12 month assessment (16 refused to participate at the onset). Such compliance in studies on pulmonary rehabilitation is rare. This study is promising in that a chronic disease management program reduced admissions and hospital bed days; however, this program is much more elaborate than pulmonary rehabilitation alone. The program study contained elements of all the following: “a COPD management guideline, a patient-specific care plan and collaboration between patients, general practitioners, practice nurses, hospital physicians and nurse specialists with conventional care, on hospital admissions and quality of life.”<sup>27</sup>

Goldstein et. al. carried out a RCT of rehabilitation comparing conventional community care to 6 months of respiratory rehabilitation and investigated the incremental costs associated with improvements in HRQL.<sup>29</sup> The

treatment group underwent 2 months of inpatient rehabilitation followed by 4 months of outpatient supervision. Of the 89 subjects 78 remained at the end of the study (38/45 in the treatment group and 40/44 in the control group). Five subjects who were withdrawn for medical reasons and two for renewal of smoking. One subjects dropped out and was noncompliant with completing the outcome measures and three others dropped out due to issues relating to travel or anxiety. No explanation was given for the exceptional compliance rate.

All costs (hospitalization, medical care, medications, home care, assistive devices, transportation) were included. In determining what defined cost, the viewpoint society was taken in that costs were included regardless of the payee: government, private insurers, or the patients. In determining the incremental cost, the investigators used improvements beyond the minimal clinically important difference. The incremental cost was \$11,597 (Canada); 90% of the cost was associated with the initial phase of hospitalization. Goldstein et. al. determined the cost-effectiveness ratio for dyspnea was \$19,011 per unit difference and \$35,142 per unit difference for fatigue. However, when looking at the minimal clinical difference, the cost required for a single patient to achieve a benefit greater than the minimal clinical difference is \$47,548 for dyspnea, and \$51,027 for fatigue.

These studies highlight the power of disease specific self-management programs that include pulmonary rehabilitation and pulmonary rehabilitation alone in terms of decreasing hospital utilization. Additionally, data obtained through health related quality of life (HRQL) measures demonstrate the

effectiveness of PR to improve the lives of patients living with COPD. HRQL measures as well as decreased patient hospital usage elevate the value of pulmonary rehabilitation. However, the efficacy of rehab is limited in its effects on mortality. As discussed in the introduction, domiciliary oxygen therapy and smoking cessation are the only therapies that have been shown to prolong survival and slow the decline of lung functioning respectively.<sup>1, 2</sup> The data are also limited in terms of the sustainability of the benefits after rehab due to the limited number of quality studies as discussed earlier in this paper..

#### **Economic Burden of COPD and the Costs of Pulmonary Rehabilitation and the Benefits**

In addition to the costs mentioned in the introduction, COPD is similar to other chronic diseases in that 10% of patients account for 73% of expenditures.<sup>3</sup> Hospitalization is one of the costliest components of the health care of patients living with COPD. The National Medical Expenditure Survey estimated hospitalizations for patients with COPD were 2.7 times as costly, per capita, as those without.<sup>3</sup>

HRQL measures and patient hospital utilization allow the medical community to better evaluate the effect and the cost-effectiveness of pulmonary rehabilitation as a treatment for COPD. The data on cost-effectiveness is limited, and while the quality on most of the studies cited above are not of high quality, the data suggest pulmonary rehabilitation is cost-effective.<sup>25</sup> Golmohammadi et. al compared the direct costs and disease-specific quality of life of patients living with COPD. The group measured cost in Canadian dollars and HRQL by the SGRQ which has been validated as detailed in the HRQL section of this

discussion. This was not a randomized controlled trial and the pre-post comparison is a weak study design, yet the results urge further investigation. When compared to the cohort who did not receive rehab, the average reduction of total costs attributed to rehab participation was \$34,367 per 100 person-years or approximately \$344 per person per year ( $p = 0.02$ ). “Over one-year, pulmonary rehabilitation was associated with decreased health service utilization, reduced direct costs and improved health status of COPD patients. This suggests that pulmonary rehabilitation is cost-effective for “patients with relatively high utilization of emergency and hospital-based services.”<sup>25</sup>

The California Pulmonary Rehabilitation Collaborative Group posits many of the previous cost-effectiveness studies were “conducted in a different era of medical practice in the United States during which it was much more common to admit patients to hospitals for treatment of exacerbations and complications of chronic lung disease”<sup>28</sup>. Newer treatments and practices use inpatient facilities less frequently for the treatment of COPD exacerbations. While it is conceivable that this previous data may have overestimated the savings from reduced hospitalizations, the group found that such suspicions were unlikely. In the group’s analysis, “there were significant and consistent reductions in important measures of resource utilization over 18 months of follow-up evaluation including hospital days, urgent care visits, physician office visits, and telephone calls to physicians.”<sup>28</sup> The most notable result of the study demonstrates an average of a 6.6 day reduction in hospital stay per hospitalized patient in the year following pulmonary rehabilitation. As stated above, the design of the study makes these

results poorly generalizable. Additionally, the sustainability of this savings is questionable as to whether it is a true cost savings or cost-shifting to a later time.

Taken apart, the quality of the studies make the results questionable and publication bias may affect the reporting of studies that show pulmonary rehabilitation is not cost-effective. However, the general trends of the studies are consistent with one another. Patients who completed pulmonary rehabilitation in one study spent an average of 10.6 less days in the hospital than the control subjects;<sup>26</sup> after PR, patient's episodes of hospital admissions per patient per year fell from 1.2 to 0.6,  $p=0.005$  and mean length of stay fell from 7.4 days to 3.3 days,  $p=0.01$  in another study.<sup>17</sup> Patients who participated in a disease management program including pulmonary rehabilitation were hospitalized nearly half as often and spent over one third less time hospitalized in the 12 months following rehab as in the 12 months prior to rehab.<sup>27</sup>

There is a measurable monetary savings associated with this reduction in hospital usage. Golmohammadi et. al. found an average reduction of total costs attributed to rehab participation of \$344 (Canadian) per person per year.<sup>25</sup> Such results suggest pulmonary rehabilitation has the potential to cut spending on hospitalizations and emergency department visits. Less decisively Griffiths et. al. suggest a similar economic benefit. The costs and benefits resulting from a 6 week outpatient rehabilitation program were studied using net cost in pounds and net utility in terms of quality adjusted life years (QALYs) gained by adding pulmonary rehabilitation to standard care. The investigators found that rehab had a 64% chance of being less expensive than providing standard care alone. While



not much better than a coin toss, by adding the QALYs gained to the analysis, Griffiths et. al. illustrate a benefit. On a purely monetary level, the trend suggests a reduction in the yearly cost of rehab when compared to standard care, but the 95% CI crosses the null: £-881 and £577. Cost reduction cannot be proven given the available data; however, Griffiths et. al. demonstrate that the upper end of a rehabilitation program is £577, with a 64% chance that rehabilitation will actually save money. In addition to the possibility of a negative cost, on average, patients undergoing rehab received 0.030 (95% CI 0.002 to 0.058) QALYs per patient.<sup>26</sup> Such data must be assessed for cost efficiency.

Even if pulmonary rehabilitation cannot achieve a cost reduction or cost neutrality, pulmonary rehabilitation has the potential to improve the HRQL and exercise capacity of patients living with COPD. A strong recommendation would have to be given to a cost neutral program that improved HRQL and increased QALYs. A large study with sufficient power or several additional smaller studies may be able to decisively prove that a cost neutral program is possible and may even prove that rehab decreases costs. Even if a cost neutral program is not possible, a low cost program that improves HRQL deserves consideration.

### **Problems with the Current Cost Measures**

The current studies have significant data that illustrate the reduction of hospital usage over one year following pulmonary rehabilitation and the improvement in HRQL for patients living with COPD during the year following pulmonary rehabilitation.<sup>2</sup> While the data are convincing for the year following

pulmonary rehabilitation, few studies investigate hospital usage after 12 months and fewer studies investigate the cost-effectiveness of rehab. The Griffiths study provides a good example of the promise of and the problems with the existing cost-effective analyses.

In the Griffiths study, the number of patients was sufficient to show that a low cost program was probable and that a cost neutral or money saving program was possible. Additionally the number of patients was sufficient to show an increase of QALYs. However, there were not enough participants to avoid using a modeling technique in order to obtain sufficient power. Additionally, the QALYs gained per patient may be artificially low due to the lower number of participants and the lack of a significant time of follow-up. However, the lack of significant follow-up time could give an artificially low cost for pulmonary rehabilitation by postponing inevitable sequelae by cost shifting these inevitable costs to a period of time beyond the study.<sup>26</sup>

Lastly, cost neutrality is not the only consideration. The medical community has a duty to improve HRQL, however limited by resources and patient autonomy.<sup>60</sup> Valuing a QALY or a point on a HRQL questionnaire in dollars is debatable, yet we must determine, either at the individual or societal level, the point at which the marginal benefit in terms of HRQL equals the marginal cost of providing that service. Until better data are collected, health care providers will have to make these decisions on an individual level with imperfect data.

### **The Studied Population**

Even the most sophisticated cost analysis is limited by the population studied. Patient recruitment and compliance with treatment are key issues in investigating pulmonary rehabilitation programs and designing randomized controlled studies to study patient outcomes following a pulmonary rehabilitation program. Compliance is an essential part of pulmonary rehabilitation. Patients have many reasons for not finishing the program or for not following up with the research team after completing a therapy. ITT allows a more realistic measure of effectiveness and provides better generalizability. Another factor that is a potential for bias is the recruitment process. Depending on the recruitment process, the study population drawn from the potential participants may be very different from the target population. In evaluating the effectiveness of pulmonary rehabilitation, especially repeat a pulmonary rehabilitation program or long term pulmonary rehabilitation, the type of patients recruited may help shape a study population that responds. One of the major limitations of the current data is that the data are gathered from only those participants that attend the programs. Very little data has ever been gathered regarding the potential candidates who did not participate either due to exclusionary criteria or by their own declination to participate.<sup>13</sup>

### **Recruitment, Enrollment, and ITT**

Recruitment information would enable providers to make better decisions for their patients living in the real world.<sup>61</sup> Patients at various levels of disability respond to pulmonary rehabilitation differently and the type of patient may

influence willingness to enroll in a study as well as attractiveness to the researches. For example, “patients with reduced exercise capacity who experience less ventilatory limitation to exercise and more reduced respiratory and peripheral muscle strength are more likely to improve with exercise training.”<sup>8</sup> Given this information, it is reasonable to question if those patients with the greatest chance of response would not be recruited due to their own lack of interest or the researchers’ own bias directed against targeting a sicker patient in the recruitment process. Such preferences would introduce bias that would move results toward the null for two significant reasons. Healthier patients may have less of a response to treatment and will appear more similar to the controls. Additionally, healthier patients may, on their own volition, exercise or practice better habits; such behavior would make the control group look more similar to the experimental group.

Dropouts, cross-overs, and patients lost to follow-up also play a large role in pulmonary rehabilitation program. A high dropout rate is evident in many studies of PRP’s. Elliot et. al. report a dropout rate of 73% at 12 months following an initial 3-month program.<sup>43</sup> and another high quality study by Brooks et. al. reports 50% of the patients did not complete the follow-up period.<sup>36</sup> Recruitment, enrolment, and compliance play a major role in introducing bias to the results of studies evaluating the effects of pulmonary rehabilitation. In a simple, yet effective, descriptive study, Young et. al. compiled data on eligible subjects who did not participate in a COPD rehabilitation program. These subjects were not more physiologically impaired, but “were more likely to be:

socially isolated, lack chronic obstructive pulmonary disease-related social support, still be smoking and be less compliant with other healthcare activities.”<sup>62</sup>

Foglio et. al. represents a study that asks a good question and has a strong study design, but fails to obtain a reliable answer due to poor recruitment practices, poor enrolment practices, and a lack of analysis on the drop-outs.<sup>37, 48</sup> The study enrolled sixty-one consecutive patients with stable chronic airway obstruction (CAO). These patients were recruited from an earlier study investigating an initial 8-week pulmonary rehabilitation program (PRP1). The recruitment and enrollment in the initial study was based upon seventy-one consecutive CAO patients in a stable condition. In the original study, complete data sets were obtained from sixty-one out of the seventy-one patients. “Six patients were lost at follow-up and four patients were excluded from the study owing to intervening physiological (one asthmatic patient became pregnant) or pathological conditions (one renal cancer, one stroke, one orthopaedic problem).”<sup>37</sup> Neither the original study paper nor the final paper discussed the recruitment any further than to state that the patients were consecutively enrolled before randomization. All the participants were ex-smokers, in stable condition, and free from exacerbations. The authors did not state whether these characteristics were intentionally recruited, part of an exclusionary or inclusionary requirement, or by chance in the final paper; however, the original paper stated that being a current non-smoker was a requirement. The authors did state they excluded patients with other organ failure or cancer, or who “were unable to cooperate.”<sup>37, 48</sup>

Response to treatment and the reasons for dropout may be affected by recruitment as could how the discharge instructions may be followed by different types of patients. After discharge from each pulmonary rehabilitation program, the patients were encouraged to perform daily life activities, but no structured exercise programs were prescribed and “after completing PRP1, patients were asked “to keep a record of hospital admissions and exacerbations for the following 2 years.”<sup>48</sup> It is reasonable to question if a more motivated patient would follow discharge instructions differently and be more prone to stay enrolled in the study. Such motivation would move the result toward to null and recruitment may have affected the motivation of the participants.

Foglio et. al. state they evaluated sixty-one CAO patients 1 year after the patients completed PRP1; however, how the investigators choose these sixty-one patients is unknown and unstated. Additionally, the original pool of seventy-one patients who were recruited for PRP1 and the group who completed PRP1 were not discussed and their numbers were never stated in the final paper. The original paper must be accessed to gain this information. Regardless, the sixty-one patients were randomly assigned either a second pulmonary rehabilitation program (PRP2) or normal care and 36 were still enrolled at the end of the study as the published flow chart illustrates (Figure 2).



functional characteristics recorded at T0, T2 (Figure 2), or, in the case of group 1, at T3” and that since “neither hospitalizations nor exacerbations in the 2 years preceding PRP1 were different between the two groups. The dropouts from the two groups were generally similar.”<sup>48</sup> Regardless, by choosing to only analyze the data from those who maintained follow up selects a specific type of patient. External validity is negatively affected as is internal validity. External validity is threatened in that the patients remaining in the study likely are not similar to the target population.

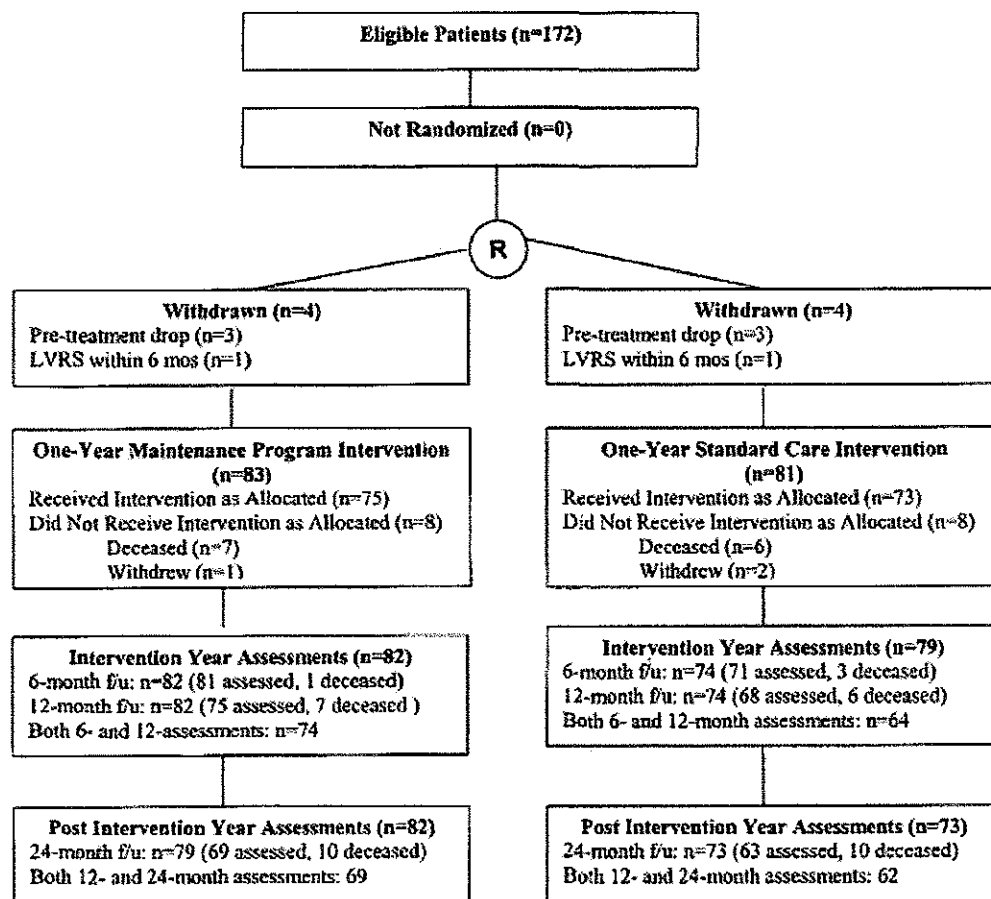
The several stages of eligibility and poor reporting make determining the eligibility fraction impossible. Even if the authors did include the number of potential participants, these participants came from a pool of previous participants with their own eligibility, enrollment, and recruitment fractions. This selection creates participants who may not represent the target population. Such selection conjures the image of salmon swimming upstream and surely, those thirty-six participants who are included in the complete data sets are quite different than the average patient contemplating repeating a pulmonary rehabilitation program.

In a second study, Ries et.al. are clearer in their criteria and from what target population participants were recruited, yet they fail to explain how the target population was approached. The investigators report “patients with chronic lung disease were recruited from University of California, San Diego (UCSD) Pulmonary Rehabilitation Program graduates.”<sup>31</sup> The selection criteria are stated, but there is no information as to the methods of recruitment and how these methods may have influenced the eligibility fraction.



Over a 4-year period, 340 patients enrolled in the pulmonary rehabilitation program, 190 patients completed the pulmonary rehabilitation program and were eligible for the study, 172 of these patients agreed to participate and were randomized to either the experimental maintenance program or standard care control for 1 year. Six patients were withdrawn due to a failure to complete required post-rehabilitation assessments before the experimental intervention and two patients had lung volume reduction surgery within 6 months. 13 patients died and 3 patients withdrew. Figure 3 illustrates these data:

Figure 3: Patient Enrollment and Assessment in Ries et.al.<sup>31</sup>



The differences between control and treatment groups may be exaggerated when one looks at who continues the rehab program after completing the

maximum number of sessions that insurance will cover. To look at patients who are already in rehab introduces a group that would be dramatically different than a control group of COPD patients not in rehab: access, means, compliance to medication regimens, quality of care, home environment, family/community support, education level, smoking status, fitness level and prior fitness level, and motivation. These many differences introduce bias affecting both internal and external validity. The cases become very different from both the general population and the controls. Due to problems with recruitment, from any control group may also become different than the general population.

## **Conclusions**

Current research is limited by quality and quantity; however, continued exercise maintenance therapy appears associated with modest improvements in exercise capacity, but not with any difference in lung function. Results were not conclusive of a benefit in HRQL or dyspnea. Further research is needed to confirm the associations and further investigate the affects of HRQL and dyspnea.

The problems with patient enrolment, recruitment, compliance, and retention rates are central in the generalizability of studies investigating pulmonary rehabilitation. Currently, the data discussed in this paper can only be generalized to patients who are willing, able, and motivated to complete rehabilitation. Further, these more motivated patients with means remain the only available subjects for rehabilitation study as those lacking the motivation or the means to attend rehabilitation will continue to dropout of or fail to participate in

physical rehabilitation. Current research is already being conducted to investigate how various modalities of rehabilitation affect motivation; however, the time and opportunity cost to the patient of rehabilitation must also be considered.

Lastly, while data suggests that pulmonary rehabilitation is cost effective, more research is needed to make this case more clearly. Further research is also needed to make a case for the cost effectiveness of exercise maintenance therapy. At present, the research does not provides enough data to make any informed statement as to the cost incurred or cost saved by a program of exercise maintenance therapy following initial rehabilitation. The findings of Ries et. al. suggest that maintenance therapy must be continued in order for benefits to be sustained. This finding will make the task of cost analysis more complicated.

In conclusion, the data suggests that continued exercise maintenance therapy is associated with modest improvements in exercise capacity; however, the cause of this improvement remains unclear. Lung function remains unchanged by continued exercise maintenance therapy. Furthermore, the results were not conclusive as to a benefit in HRQL or dyspnea. The selection and recruitment bias that exists within the studies regarding pulmonary rehabilitation weakens the generalizability of the data reported. Further research is needed to confirm the associations and further investigate the affects of HRQL and dyspnea following pulmonary rehabilitation and maintenance therapy.

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